DOI: 10.15826/chimtech.2016.3.1.007

Vladimir V. Tkach[1,2], Silvio C. de Oliveira[2], Severino K.B. de Oliveira[3], Reza Ojani[4], O.V. Elenich[1], P. I. Yagodynets´[1]

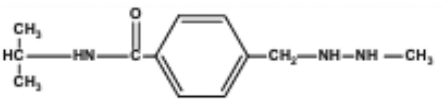
[1]Chernivtsi National University, Ukraine
[2]Federal University of Mato Grosso do Sul, Brazil
[3]Federal Agricultural University of Pernambuco, Brazil
[4]Mazandaran University, Islamic Republic of Iran
E-mail: nightwatcher2401@gmail.com

The mechanism for the electrooxidation of procarbazine pharmaceutical preparation in alkaline media and its mathematical description

The mechanism for the electrooxidation of procarbazine in alkaline media has been proposed. The process is realized completely on the electrode surface and is adsorption-controlled. The oscillatory behavior in this case is more probable, than for neutral media and may be caused by influences of electrochemical oxidation and salt dissolution from the electrode surface.

Introduction

Procarbazine, i.e. N-isopropyl-α-(2-methylhydrazino)-p-toluamide is one of the drugs commonly used in chemotherapy at different types of cancer [1–2].



The exact mechanism of action of the pharmaceutical preparation is still not determined. However, it is already known that its interaction with various substances (such as enzymes or compounds of transition metals) in the human organism leads to the formation of toxins (aldehydes, hydrazine and metal complexes) [3]. Therefore, search of sensitive, precision and expeditious method for determining the concentration of the compound is a really actual task [4].

On the other hand, the use of electrochemical methods of analysis is one of reliable modern approaches to pharmaceutical (and not only) analytics since it has advantages over spectral and chromatographic methods such as sensitivity, accuracy, easy interpretation of the analytical signal and speed of analysis [5–10]. However in some cases there occur problems of high anode voltage, the lack of data on the most likely mechanism for the electrooxidation of preparation and

electrochemical instabilities characteristic of the electrooxidation of small organic molecules (including electropolymerization of heterocyclic compounds) and hydrogen [11–16].

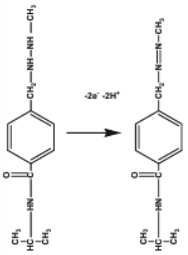
In the case of procarbazine the main problem is the small amount of data on the electrooxidation of said compound [4, 17] and a lack of theoretical works on the subject. In [4] an attempt to determine based on a purely experimental data the mechanism of the electrooxidation of the preparation under neutral conditions has been made. However the study was hindered by the lack of a solid theoretical foundation which is provided only as a result of construction and analysis of mathematical model that can adequately describe this process.

The aim of this work is the mechanistic study of the procarbazine electrooxidation in alkaline medium. Achievement of this aim is based on achieving the following specific objectives: the construction of a mathematical model, the analysis of the mathematical model, the study of steady state stability conditions and electrochemical instabilities (self-oscillatory or monotonic) and the comparison of the behavior of the system with the behavior of ones similar to it [18–21].

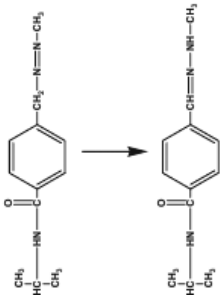
System and its model

According to [4] the procarbazine electrooxidation consists in four steps:

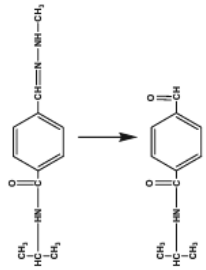
1. Oxidation of procarbazine to an azo derivative:



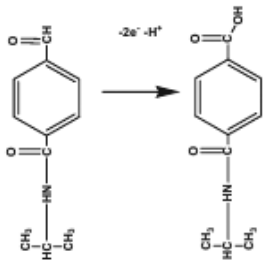
2. Isomerization of the azo derivative in a Schiff base:



3. Hydrolysis of the Schiff base to form an aldehyde:



4. Electrooxidation of the aldehyde to form terephthalic acid N-isopropyl monoamide (in alkaline media a salt is formed):



Since the electrochemical reactions occur with elimination of proton in alkaline medium, they must occur faster than in neutral medium.

The process takes place entirely at the anode surface and it can shown that the behavior of the system in this case is described by the following system of equations:

$$\begin{cases} \dfrac{d\theta_1}{dt} = \dfrac{1}{G}(r_1 - r_2) \\ \dfrac{d\theta_2}{dt} = \dfrac{1}{H}(r_2 - r_3) \\ \dfrac{d\theta_3}{dt} = \dfrac{1}{J}(r_3 - r_4) \end{cases} \quad (1)$$

wherein parameters θ being the anode filling degree with the azo compound, the Schiff base and the aldehyde, G, H and J being their maximum surface concentrations and parameters r being velocities of corresponding reactions can be calculated according to the following equations:

$$r_1 = k_1(1-\theta_1-\theta_2-\theta_3)\exp\left(\frac{2F\varphi_0}{RT}\right)$$
$$r_2 = k_2\theta_1$$
$$r_3 = k_3\theta_2 \quad (2–5)$$
$$r_4 = k_4\theta_3 \exp\left(\frac{2F\varphi_0}{Rt}\right)\exp(-a\theta_3)$$

Results and discussion

In order to investigate the behavior of the system with the procarbazine electrooxidation in alkaline medium, the system of differential equations (1) taking into account algebraic relations (2–5) using a linear stability theory has been analyzed. The functional Jacobi matrix, whose elements are calculated for steady state, is written as follows:

$$\begin{pmatrix} g_{11} & g_{12} & g_{13} \\ g_{21} & g_{22} & g_{23} \\ g_{31} & g_{32} & g_{33} \end{pmatrix} \quad (6)$$

wherein:

$$g_{11} = \frac{1}{G}\left(-k_1\exp\left(\frac{2F\varphi_0}{RT}\right) + jk_1(1-\theta_1-\theta_2-\theta_3)\exp\left(\frac{2F\varphi_0}{RT}\right) - k_2\right)$$

$$g_{12} = \frac{1}{G}\left(-k_1\exp\left(\frac{2F\varphi_0}{RT}\right) + lk_1(1-\theta_1-\theta_2-\theta_3)\exp\left(\frac{2F\varphi_0}{RT}\right)\right)$$

$$g_{13} = \frac{1}{G}\left(-k_1\exp\left(\frac{2F\varphi_0}{RT}\right) + mk_1(1-\theta_1-\theta_2-\theta_3)\exp\left(\frac{2F\varphi_0}{RT}\right)\right)$$

$$g_{21} = \frac{1}{H}(k_2) \quad g_{22} = \frac{1}{H}(-k_2) \quad g_{22} = 0$$

$$g_{31} = \frac{1}{J}\left(-jk_4\theta_3\exp\left(\frac{2F\varphi_0}{RT}\right)\right) \quad (7–15)$$

$$g_{32} = \frac{1}{J}\left(k_3 - lk_4\theta_3\exp\left(\frac{2F\varphi_0}{RT}\right)\right)$$

$$g_{33} = \frac{1}{J}\left(-k_4\exp\left(\frac{2F\varphi_0}{RT}\right)\exp(-a\theta_2) - mk_4\theta_3\exp\left(\frac{2F\varphi_0}{RT}\right)\exp(-a\theta_3) + ak_4\theta_3\exp\left(\frac{2F\varphi_0}{RT}\right)\exp(-a\theta_3)\right)$$

Self-oscillating instability of the system is possible since necessary conditions of Hopf bifurcation can be fulfilled in fact in the main diagonal of Jacobian there are positive elements responsible for the

positive feedback. In addition to element $ak_4\theta_3 \exp\left(\frac{2F\varphi_0}{RT}\right)\exp(-a\theta_3)$ responsible for self-oscillations when attracting the adsorbed molecules of a salt during its passing into a solution, members $lk_1(1-\theta_1-\theta_2-\theta_3)\exp\left(\frac{2F\varphi_0}{RT}\right)$ and $-mk_4\theta_2 \exp\left(\frac{2F\varphi_0}{RT}\right)\exp(-a\theta_3)$ describing self-oscillations caused by influence of electrochemical processes on the structure of the electrical double layer (EDL) may also have positive values. These factors are the cause of the self-oscillatory behavior for other similar systems [19–21], but it should be noted that if for alkaline medium both factors are possible then for neutral medium, in which the salt formation and passing of the acid anion in the solution does not virtually take place, only the latter factor is the cause of the self-oscillatory behavior.

Steady state stability study on the basis of the Routh-Hurwitz criterion shows that said reaction is controlled by a procarbazine adsorption factor as well as the state of the EDL during the reaction. If in order to avoid cumbersome mathematical expressions to enter new variables so that the determinant of the Jacobian matrix is written as follows:

then at the opening parenthesis the condition Det $J<0$ will be written as follows:

$$\frac{1}{GHJ}\begin{vmatrix} -\kappa_1-k_2 & -\Pi & -\Phi \\ k_2 & -k_3 & 0 \\ -K & k_3-\theta & -P \end{vmatrix} \qquad (16)$$

$$-\Phi(k_2k_3 - k_2\theta - Kk_3) - \\ -P(\kappa_1k_3 + k_2k_3 + \Pi k_2) < 0 \qquad (17)$$

This inequality is guaranteed to be satisfied if parameters Φ, κ, Π, θ and K describing the influence of electrochemical reactions on the EDL as well as the interaction of adsorbed molecules in salt formation and passing to the solution are positive that is achieved by the absence or weakness of influences of electrochemical reactions on the structure of the EDL and by the repulsive interaction of adsorbed molecules. In this case the left-hand side of the inequality reaches more negative values. Since chemical and electrochemical reactions described above are faster than the procarbazine adsorption onto the anode surface the process is controlled by the procarbazine adsorption

In case of equality of the influence of destabilizing and stabilizing factors on the stability of the steady state then *monotonic instability* appears which is presented as N-shaped segment in a voltammogram. The condition of its appearance is described as follows:

$$-\Phi(k_2k_3 - k_2\theta - Kk_3) - \\ -P(\kappa_1k_3 + k_2k_3 + \Pi k_2) = 0 \qquad (18)$$

Conclusion

In alkaline medium the procarbazine electrooxidation to some extent is faster than in neutral medium but appearance of self-oscillations in it is more likely due to the presence of a salt formation factor and dissolution of the salt of terephthalic acid N-isopropyl monoamide. The reaction itself is controlled by the procarbazine adsorption and the state of the EDL.

1. Newton H. B. Handbook of Brain Tumor Chemoterapy. Elsevier, 2006

2. Shiba D. A., Weinkam R. J. The in vivo cytotoxic activity of procarbazine and procarbazine metabolites against L1210 ascites leukemia cells in CDF1 mice and the effects of pretreatment with procarbazine, phenobarbital, diphenylhydantoin, and methylprednisolone upon in vivo procarbazine activity. *Cancer Chemoter. Pharmacol.* 1983;11(2):124-129. DOI: 10.1007/BF00254261.
3. Aronson J. K. Meyler's Side Effects of Drugs in Cancer and Immunology. Elsevier, 2010
4. Oliveira S. C. B., Mendes C. H. S., Filho F. F. S., Queiroz N. L.,Nascimento J. A. M., Nascimento V. B. Electrochemical oxidation mechanism of procarbazine at glassy carbon electrode. *J. Electroanal. Chem*. 2015;746(1):51-56. DOI: 10.1016/j.jelechem.2015.02.033.
5. Mahanthesha K. R., Swamy B. E. K., Pai K.V. Poly (alizarin) modified glassy carbon electrode for the electrochemical investigation of Omeprazole: A voltammetric study. *Anal. Bioanal. Electrochem.* 2014;6(2):234-244.
6. Ojani R., Raoof J., Ahmady A., Hosseini S. R. *Casp. J. Chem*. 2013;2:45.
7. Raoof J., Ojani R., Hosseini S. R. An electrochemical investigation of methanol oxidation on nickel hydroxide nanoparticles. *South Afr. J. Chem*. 2013;66:47-53.
8. Ojani R., Raoof J. B., Zavvarmahalleh S. R. H. Electrocatalytic oxidation of methanol on carbon paste electrode modified by nickel ions dispersed into poly (1,5-diaminonaphthalene) film. *Electrochimica Acta*. 2008;53(5):2402-2407. DOI: 10.1016/j.electacta.2007.10.004.
9. Shu H. Applications of poly(3-hexylthiophene) thin film as a hydrazine-sensitive chemoresistor. M. Sc. Thesis. Alburn. Alabama, 2006
10. Tosar J. P. Rovira. Estudio de la inmovilización de oligonucleótidos a eléctrodos modificados de oro:polipirrol, y detección electroquímica de secuencias complementarias. Tes. Lic. Bioquím. Universidad de la República. Montevideo, 2008.
11. Pagitsas M., Sazou D. The improved Franck-FitzHugh model for the electrodissolution of iron in sulphuric acid solutions: linear stability and bifurcation analysis. Derivation of the kinetic equations for the forced Franck-FitzHugh model. *Electrochimica Acta*. 1991;36(8):1301-1308. DOI: 10.1016/0013-4686(91)80009-W.
12. A. J. Pearlstein, J. A. Johnson. *J. Electrochem. Soc*. 1991;136:1290.
13. Das I., Agrawal N. R., Ansari S. A., Gupta S. K. Pattern formation and oscillatory electropolymerization of thiophene. *Ind. J. Chem*. 2008;47(12):1798-1803.
14. Rahman S. U., Ba-Shammakh M. S. Thermal effects on the process of electropolymerization of pyrrole on mild steel. *Synth. Met*. 2004;140(2-3):207-223. DOI: 10.1016/S0379-6779(03)00369-2.
15. Liu A. S., Oliveira M. A. S. Electrodeposition of polypyrrole films on aluminum from tartrate aqueous solution. *J. Braz. Chem Soc*. 2007;18(1):143-152.
16. Sazou D. The dynamical behavior of the electrochemical polymerization of indole on Fe in acetonitrile-water mixtures. *Synth. Met*. 2002;130(1):45-54. DOI: 10.1016/S0379-6779(02)00110-8.
17. McCue J. P., Kennedy J. H. Oxidation of procarbazine in the presence of Ti(IV). Bioinorg. Chem. 1977;7(1):5-21. DOI: 10.1016/S0006-3061(00)80125-8.
18. Tkach V., Kumara Swamy B., Ojani R. et. al. *Orbital Elec. J. Chem*. 2015;7:1.
19. Tkach V., Ojani R., Nechyporuk V., Yagodynets´ P. *Rev. Fac. Ing. UCV*. 2015;30:65.
20. Tkach V., Nechyporuk V., Yagodynets P. *Med. J. Chem*. 2015;3:1122.
21. Tkach V. V., Nechyporuk V. V., Yagodynets´ P. I., Kushnir V. M. *Afinidad*. 2015;72:218.